

Diagnostics in the COVID-19 Pandemic Response: use of serology tests

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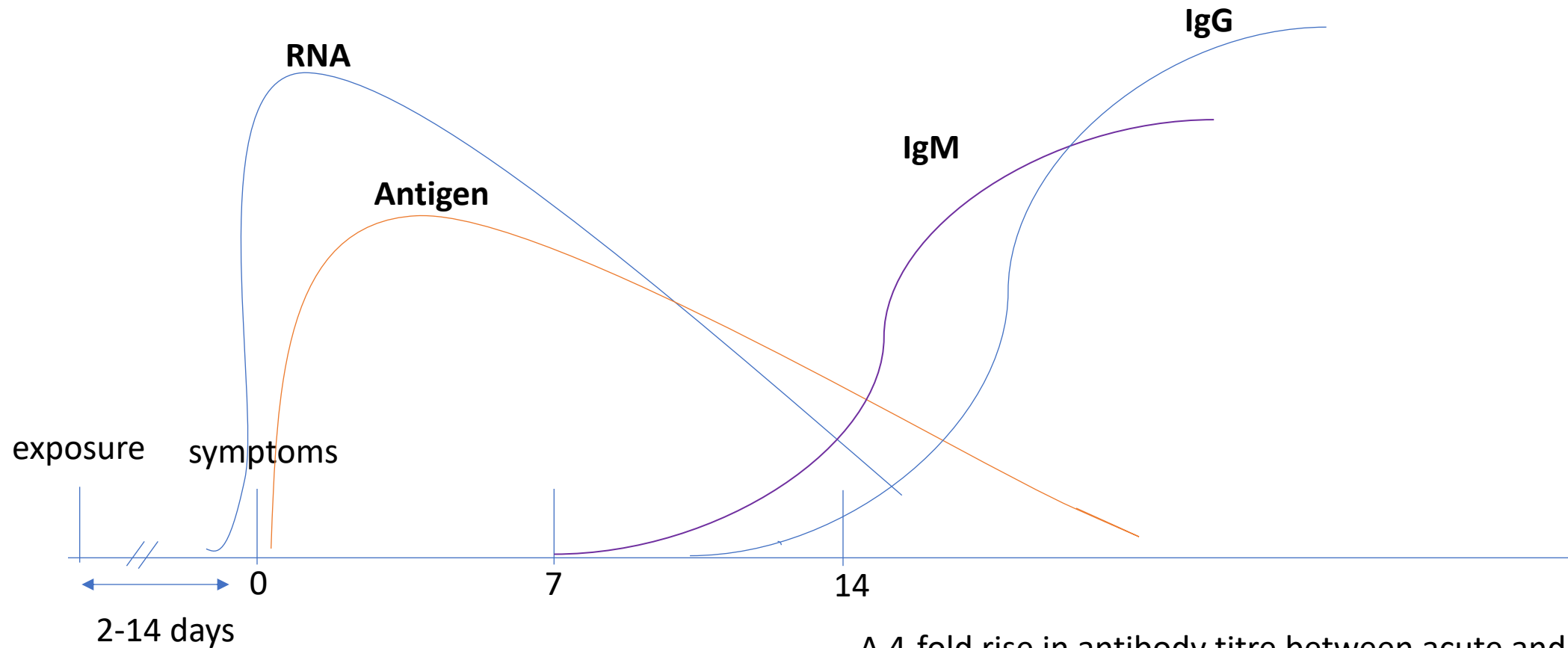
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Viral Infection and Immune Response Dynamics



A 4-fold rise in antibody titre between acute and convalescent sera = definite diagnosis





What do we know about SARS-CoV-2 infectivity and RNA detection?

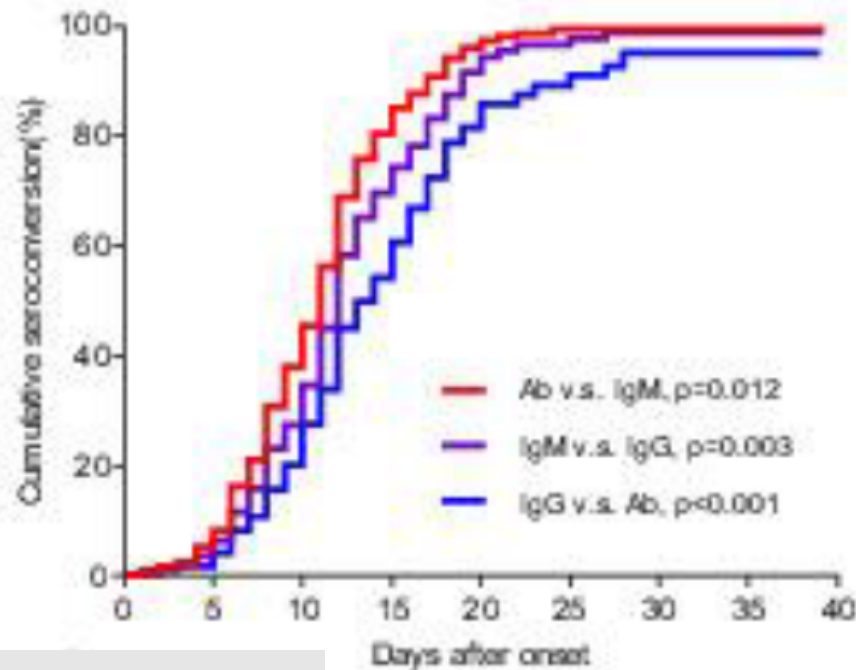
- SARS-CoV-2 RNA can be detected 1-2 days before onset of symptoms and can remain detectable up to 25-50 days post onset of symptoms, esp in patients not showing signs of recovery (To et al 2020)
- Viral RNA levels peak within the first 5 days post onset of symptoms and decrease slowly with rising antibody levels
- RNA clearance is not always correlated with rising antibody levels, especially in those who were critically ill
- One study (n=9) showed that, viral mRNA was only detectable 5-7 days post onset of symptoms but RNA tests remain positive for 1-2 weeks (Wolfel et al 2020)



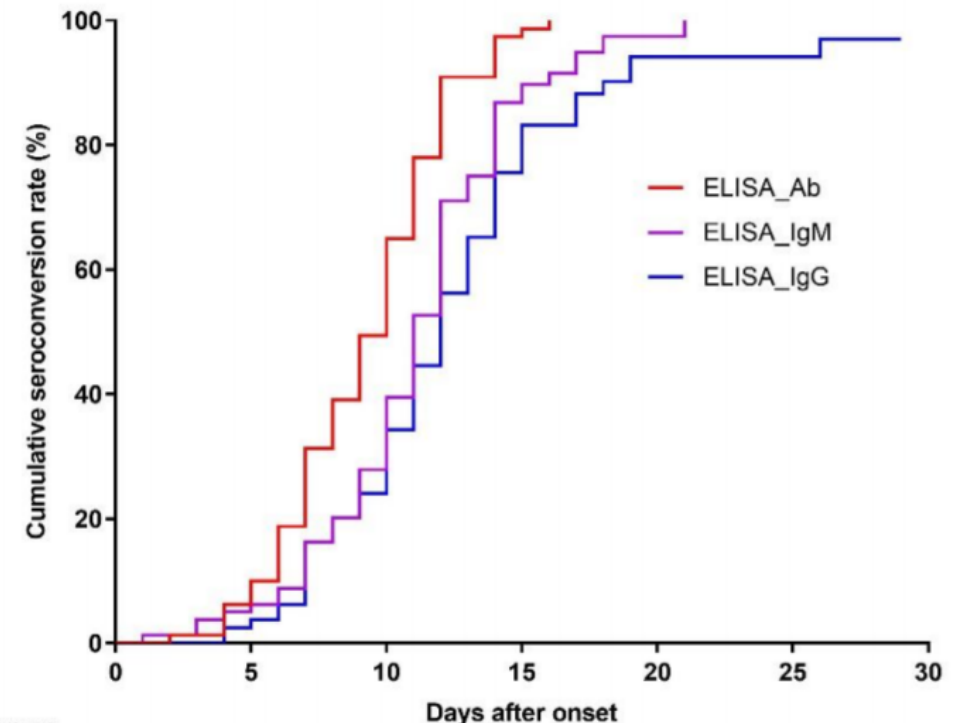


What do we know about the Immune Response to COVID-19?

- Maturation of the immune response takes ~ 40 days
- Seroconversion is typically within the first 3 weeks; mean time for seroconversion: total Ab= d. 11; IgM= d. 12; IgG: d. 14



Zhao et al CID 2020, N=173



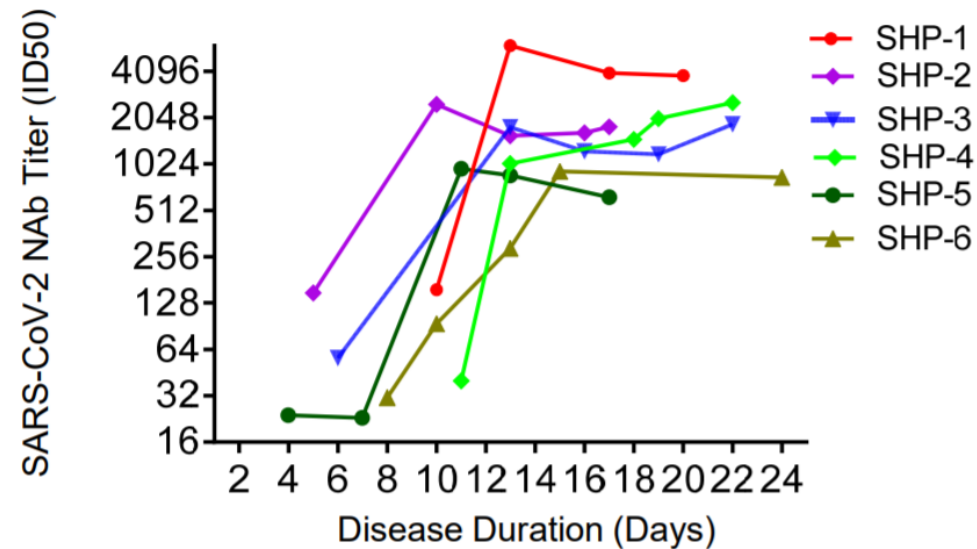
Lou et al MedRxiv mar 2020, N=80



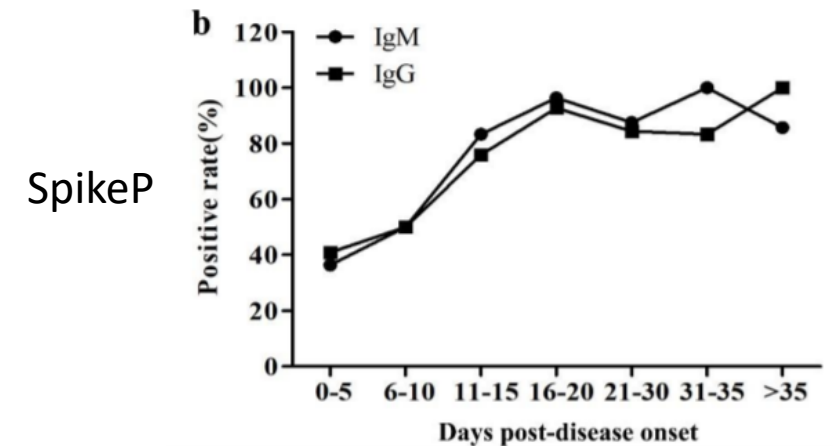
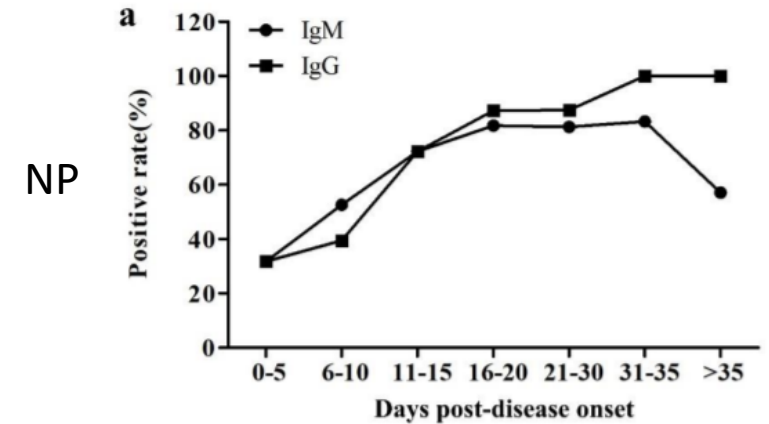


What do we know about neutralising antibody response to COVID-19?

- Antibodies against the Receptor Binding Domain (RBD) of the Spike protein and the nucleocapsid protein (NP) are correlated with neutralising activity

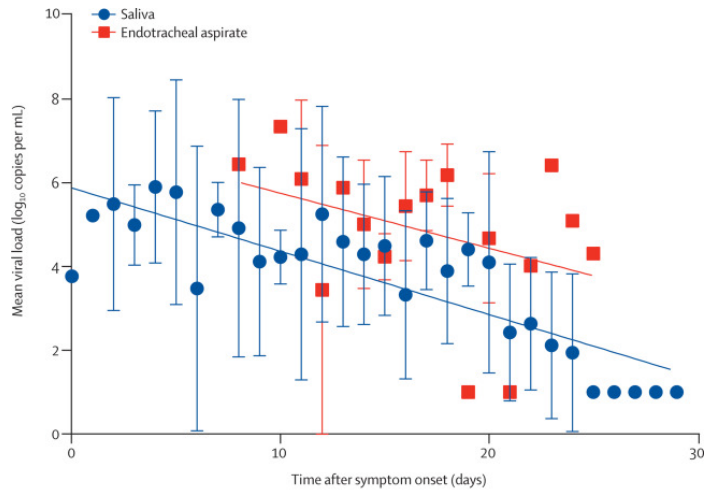


Wu et al. MedRxiv mar 2020



Liu et al J Clin Microbiol Mar 2020, N=214

Viral Load and Antibody Responses in Hospitalised COVID-19 Patients

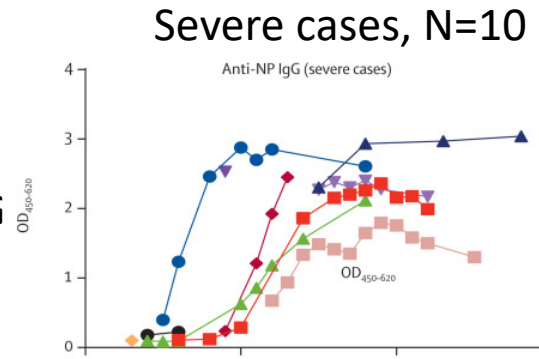


To et al. Lancet Infect Dis Mar 2020

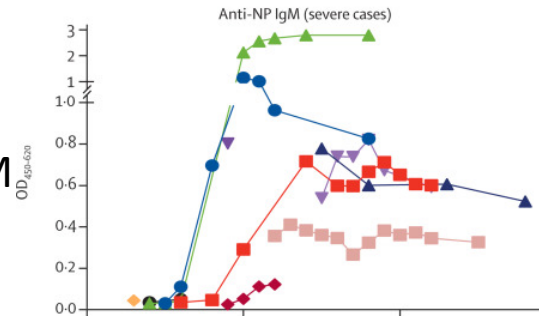
Severe cases were more frequently found in patients with high IgG levels compared to those with low levels (52% vs 32%, $p=0.008$)

Ref: Zhang et al MedRxiv, N=222 patients

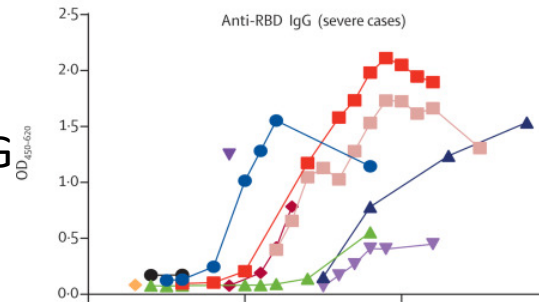
Anti-NP IgG



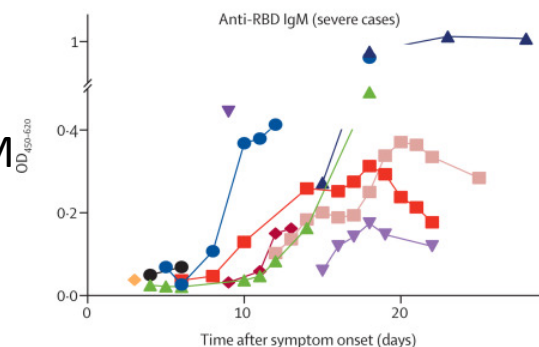
Anti-NP IgM



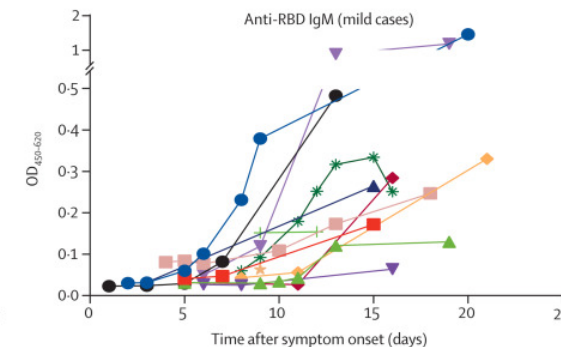
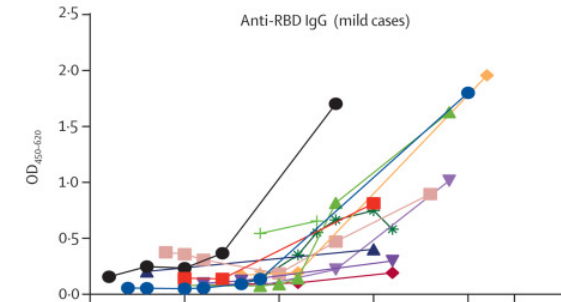
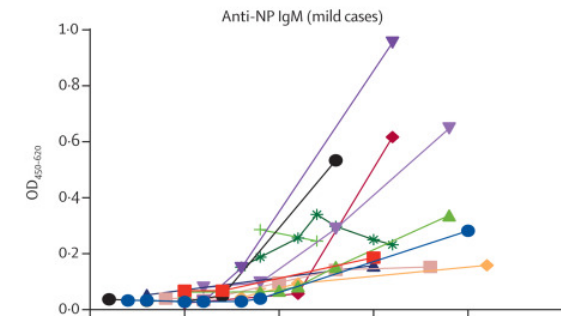
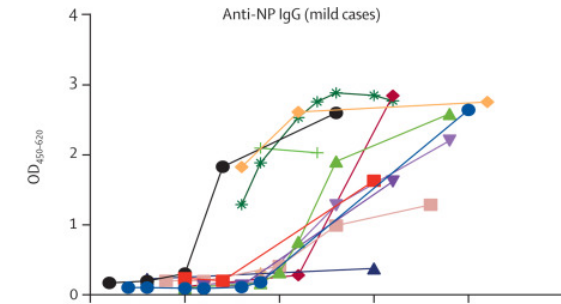
Anti-RBD IgG



Anti-RBD IgM



Mild cases, N=13



Combining RNA + Serology Tests Improves Sensitivity of COVID-19 Diagnosis

Day post onset	# patients	RNA+ (%)	Total AB+ (%)	IgM+ (%)	IgG+ (%)	RNA +Ab
1-7	94	66.7	38.3	28.7	19.1	78.7
8-14	135	54.0	89.6	73.3	54.1	97.0
15-39	90	45.5	100	94.3	79.8	100



Advice on the use of point-of-care immunodiagnostic tests for COVID-19

Scientific brief

8 April 2020



World Health
Organization

In response to the growing COVID-19 pandemic and shortages of laboratory-based molecular testing capacity and reagents, multiple diagnostic test manufacturers have developed and begun selling rapid and easy-to-use devices to facilitate testing outside of laboratory settings. These simple test kits are based either on detection of proteins from the COVID-19 virus in respiratory samples (e.g. sputum, throat swab) or detection, in blood or serum, of human antibodies generated in response to infection.

WHO applauds the efforts of test developers to innovate and respond to the needs of the population.

However, before these tests can be recommended, they must be validated in the appropriate populations and settings. Inadequate tests may miss patients with active infection or falsely categorize patients as having the disease when they do not, further hampering disease control efforts. **At present, based on current evidence, WHO recommends the use of these new point-of-care immunodiagnostic tests only in research settings. They should not be used in any other setting, including for clinical decision-making, until evidence supporting use for specific indications is available.**

WHO continues to evaluate available immunodiagnostic tests for COVID-19 and will update this scientific brief when necessary.



Diagnostics Tests: Understanding the 3 As

Diagnostic Tests	Target	Accuracy		Accessibility	Affordability	Optimal Detection (post onset of symptoms)
		Sens	Spec			
Molecular	RNA	***	***	√	\$\$\$	Day 0-7
Antigen(s)	Proteins	**	**	√√	\$\$	Day 0-10
Serology	Antibody	***	**	√√√	\$	Day 7-40



Possible Uses of Rapid Serology Tests

1. **Rapid triage** of suspect cases in the community
2. **Test contacts** of confirmed cases
3. **Situation analysis and Surveillance**
4. **Discharge** of COVID-19 patients from hospital
5. **“Immunity passport”** for health care workers to return to work



1. Rapid Triage of Suspect Cases in Peru

Population: 32 million; limited molecular testing facilities and only 500 ICU beds

- A hotline and website ran by the MOH allow those who have symptoms to call/connect
- After a short interview with a health professional, a visit for testing the symptomatic and contacts at home is scheduled, prioritizing visits according to age and risk factors and severity of symptoms:
 - Those who are IgM/IgG positive and whose symptoms are mild are quarantined at home or are taken to a quarantine facility
 - Those who need critical care are referred to hospital
 - Those who test negative have a swab collected for molecular testing
- As of April 18th, 135,895 people have been triaged with 14, 420 positives. This approach has allowed a large number of symptomatic individuals to be rapidly tested in the community, relieving the backlog and waiting time for molecular testing and preventing the health care system from being overwhelmed.

(<http://elbuho.pe/2020/04/coronavirus-peru-ultimas-noticias-y-casos/>)



2. Test Contacts of Confirmed COVID-19 Cases

- Studies have shown that a large number of infected individuals may have only mild symptoms or no symptoms at all but they can still shed virus and transmit infection
- Experience from Singapore showed that tracking down all contacts of confirmed COVID-19 cases, testing them for evidence of infection, regardless of symptoms, and putting those who test positive into isolation is an urgent priority for containing the epidemic, esp in the early stages when there are only sporadic or clusters of cases.
- Testing all contacts of a confirmed case, regardless of symptoms, is critical in interrupting the chain of transmission in the community:
 - those who test positive should self-isolate
 - those who test negative should have a throat swab collected for molecular testing



3. Situation Analysis and Surveillance

- Test samples collected through syndromic surveillance programmes:
 - Severe Acute Respiratory Infection (SARI) surveillance
 - Influenza-like illness (ILI) through National Influenza Sentinel Surveillance System
- If these sentinel sites are representative of the population, then serology testing can be used to:
 - estimate the true extent of the pandemic
 - map its geographic distribution and identify hotspots
 - Determine the attack rate and at risk populations
 - monitor trends over time
- These results can be used to inform public health measures



4. Discharge of Recovered COVID-19 cases from Hospital?

- The optimal criteria for hospital discharge are 2 negative molecular tests over several days
- Hospital beds are often in short supply and molecular testing may be limited or not available
- Some patients remain RNA positive despite having rising levels of IgM and IgG antibodies
- Some patients in a small study remained RNA positive even when virus replication has stopped; uncertainty as to whether immune patients can shed infectious virus remains



5. Immunity Passports?

- Can serology tests be used to determine whether essential workers, esp. health care workers, who has recovered from COVID-19 return to work?
- COVID-19 patients can remain RNA positive despite rising levels of neutralising antibodies
- Some studies have also reported that high IgG levels are associated with severe disease
- Protective immunity is not well understood. Hence what type of tests can be used to give an “Immunity Passport” remains unclear





WORLD BANK GROUP

Research & Policy Briefs

From the World Bank Malaysia Hub

No. 29

April 8, 2020

How Two Tests Can Help Contain COVID-19 and Revive the Economy

Damien de Walque, Jed Friedman, Roberta Gatti, and Aaditya Mattoo

Faced with COVID-19, countries are taking drastic action based on little information. Two tests can help governments shorten and soften economically costly suppression measures while still containing the novel coronavirus (COVID-19) pandemic. The first—a PCR assay—identifies people currently infected by testing for the presence of live virus in the subject. The second—an antibody test—identifies those rendered immune after being infected by searching for COVID-19-specific antibodies. The first test can help contain the disease because it facilitates the identification of infected persons, the tracing of their contacts, and isolation in the very early stages of an epidemic—or after a period of suppression, in case of a resurgent epidemic. The second can help us assess the extent of immunity in the general population or subgroups, to finetune social isolation and to manage health care resources. Wide application of the two tests could transform the battle against COVID-19, but implementing either on a large scale in developing countries presents challenges. The first test is generally available, but needs to be processed in adequately equipped laboratories with trained staff. The second test is easy to perform and can be processed quickly on the spot, but at this stage it is produced and available only on a limited basis in a few countries. This policy brief reviews the use of both tests, suggests strategies to target their use, and discusses the benefits and costs of such strategies. If PCR assay testing, together with tracing and isolation, helps reduce the duration of suppression measures by two weeks, and antibody testing allows one-fifth of the immune return to work early, the gain could be about 2 percent of national income, or about \$8 billion for a country like the Philippines. Because the estimated economic benefits of the tests are likely to far outweigh the cost, the international community must help countries develop the capacity to process the first test and procure the second.

“The social returns to gathering...information and acting upon it is high: it reduces both the death toll and the size of the economic contraction.”

—Eichenbaum, Rebelo, and Trabandt (2020)



Summary: Possible Uses of Rapid Serology Tests

1. **Rapid triage** of suspected cases in the community
2. **Test contacts** of confirmed cases
3. **Situation analysis and Surveillance**

Not recommended:

4. **Discharge** of COVID-19 patients from hospital
5. **“Immunity passport”** for health care workers to return to work



Acknowledgement

**LSHTM/IDC: David Heymann, Catherine Wedderburn, Debi Boeras,
Noah Fongwen**

Africa CDC: John Nkengasong, Yenew Kebede

Institut Pasteur Dakar: Amadou Sall

ASLM: Ndlovu Nqobile, Pascale Ondo

FIND: Sergio Carmona, Jilian Jacks, Cassandra Kelly

Cayetano University, Peru: Patricia Garcia

Federal University Rio de Janeiro, Brazil: Amilcar Tanuri

Xiao-Chun Wang and many others

